

# Alerts, Notices, and Case Reports

## Spinal Brucellosis in a Southern California Resident

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BRUCELLOSIS IS A disease of both domestic and wild animals caused by infection with small gram-negative coccobacilli of the genus *Brucella*.<sup>1</sup> The organism can be transmitted to humans, producing the zoonosis sometimes referred to as "Malta fever" or "undulant fever." Rare in the United States since the implementation of mandatory pasteurization of milk products in the 1940s, human brucellosis is reportable in every state except Nevada.<sup>2</sup> Due in part to the nonspecific clinical manifestations of *Brucella* species infection, only an estimated 4% to 10% of cases are recognized and reported.<sup>3</sup>

In the United States, brucellosis has most often been described as an occupational disease primarily affecting adult men with exposure to the organism through work with livestock or animal products.<sup>1,4,5</sup> Groups traditionally at increased risk have included workers in the meat-packing industry and laboratory personnel who handle *Brucella* specimens.<sup>4</sup> In contrast, brucellosis was originally described as and remains a predominantly food-borne illness in much of the world, affecting both sexes and patients of all ages.<sup>1</sup> In California, epidemiologic data suggest that there has been a shift in the past decade, as brucellosis is much more likely to be a food-borne infection acquired in Mexico or from Mexican food products (such as unpasteurized dairy products) rather than an occupational illness.<sup>6</sup> Our recent experiences with patients presenting to the Olive View-University of California, Los Angeles (UCLA), Medical Center certainly appear to support this trend in food-borne acquisition.

As the regional epidemiology of brucellosis changes, physicians must reacquaint themselves with the clinical spectrum and salient features that distinguish the disease from other systemic febrile illnesses. Although a purely clinical diagnosis is often difficult given the insidious and nonspecific signs and symptoms that characterize infection with *Brucella* species, certain disease patterns should warrant further diagnostic laboratory investigation. Although commonly a nonspecific systemic illness, human brucellosis may manifest with localized disorder of a specific organ system or tissue.<sup>1,7-9</sup> Such "focal" brucellosis

frequently involves osteoarticular structures, the central nervous system, heart, liver, and spleen.<sup>1</sup> Infection localizing to osteoarticular structures is one of the most common and well-studied complications of human brucellosis.<sup>1,10,11</sup> Osteoarticular complications manifest in a characteristic pattern that may aid in the clinical diagnosis.

The following case, demonstrating several classic features of osteoarticular brucellosis, was seen at the Olive View-UCLA Medical Center, a Los Angeles County hospital facility that serves a large Latino population among the greater patient population of Los Angeles County.

### Report of a Case

The patient, a 54-year-old man, presented to the emergency department because for two months he had had lower back pain radiating to the posterior aspects of the lower extremities. The patient had increasing difficulty walking because of pain and also had had a 12-kg (25-lb) weight loss over the past two months. There was no history of fevers, chills, sweats, gastrointestinal symptoms, cough, or trauma. The patient said that he had recently traveled to Mexico, where he was diagnosed with diabetes mellitus. He was currently taking an unknown medication.

On examination in the emergency department, the patient was afebrile. The only pertinent findings included tenderness over the second to the fourth lumbar vertebrae and a small prostatic nodule. A neurologic examination elicited no abnormalities. Pertinent laboratory values were as follows: leukocyte count,  $6.0 \times 10^9$  per liter (6,000 per mm<sup>3</sup>); hemoglobin, 140 grams per liter (14.0 grams per dl); hematocrit, 0.43 (43%); platelet count,  $242 \times 10^9$  per liter; serum glucose, 9.4 mmol per liter (170 mg per dl [normal, 3.9 to 6.1 mmol per liter]); and alanine aminotransferase, 36 U per liter. Normal values were obtained for serum electrolytes, blood urea nitrogen, creatinine, calcium, aspartate aminotransferase, total bilirubin, alkaline phosphatase, and total protein levels. A Westergren erythrocyte sedimentation rate was 61 mm per hour. A prostate-specific antigen test was done.

A plain film of the lumbosacral spine, pelvis, and hips revealed osteophytes of the L-4, L-5, and S-1 vertebrae. There was no evidence of fracture. Magnetic resonance imaging (MRI) revealed signs compatible with osteomyelitis of the L-4 and L-5 vertebral bodies with accompanying discitis and the presence of an epidural abscess (Figure 1). Blood specimens were drawn for culture, and a purified-protein derivative skin test and controls were placed. After a neurosurgical evaluation, the patient was admitted to the hospital for an operative procedure based on the clinical impression of "epidural abscess" and probable compression at the L4-5 disc space.

On admission, a total body bone scan (using technetium Tc 99m sulfur colloid) revealed increased radio-tracer uptake at the L-5 vertebra and the left sacroiliac joint (Figure 2). A regimen of cefazolin sodium, 2 grams by intravenous piggyback every eight hours, was started,

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**ABBREVIATIONS USED IN TEXT**

MRI = Magnetic resonance imaging  
 UCLA = University of California, Los Angeles

and the infectious diseases and urology services were consulted. The patient remained clinically unchanged, with continuing lower back pain for a week. Antimicrobial therapy was switched to vancomycin hydrochloride and gentamicin sulfate. The prostate-specific antigen test result returned at 2.1 ng per ml (normal, 0 to 4 ng per ml), and the purified-protein derivative skin test and controls were negative.

On hospital day 8, an MRI was again done and revealed interval increased involvement of L-4 and L-5 vertebrae and the intervertebral disc at L4-5. There was no increased epidural encroachment. The following day, aspiration and biopsy of the left sacroiliac joint and of the vertebral "mass" obtained tissue that was submitted for culture for acid-fast bacilli, fungi, and bacteria, Gram's staining, and examination.

On day 12, the patient began having temperatures to 38.9°C (102°F). Low-grade fevers continued for the next two weeks despite the implementation of broad-spectrum antibiotic therapy. Throughout this period, all cultures and stains remained negative, as did tests for the human immunodeficiency virus, syphilis, and cryptococcal antigen. Serologic tests for coccidioidomycosis were also negative, and biopsy specimens showed no inflammatory cells or granuloma. Transrectal biopsy of the prostate nodule revealed only benign tissue. On day 23, the patient had a temperature of 37.8°C (100°F), and he complained of increasing lower back pain. An infectious diseases consultant recommended that a serum specimen be sent for *Brucella* species titers.

On day 34, results of a serum agglutination test returned, indicating a serum *Brucella* antibody titer of 1:1,280 (normal <1:64). An oral regimen of doxycycline hyclate, 100 mg twice a day, and rifampin, 450 mg twice a day, was started. The patient was discharged two days later with the diagnosis of *Brucella* species vertebral osteomyelitis and anterior epidural abscess. With continued antimicrobial therapy, he had a dramatic reduction in back pain and improved mobility over the following six months.

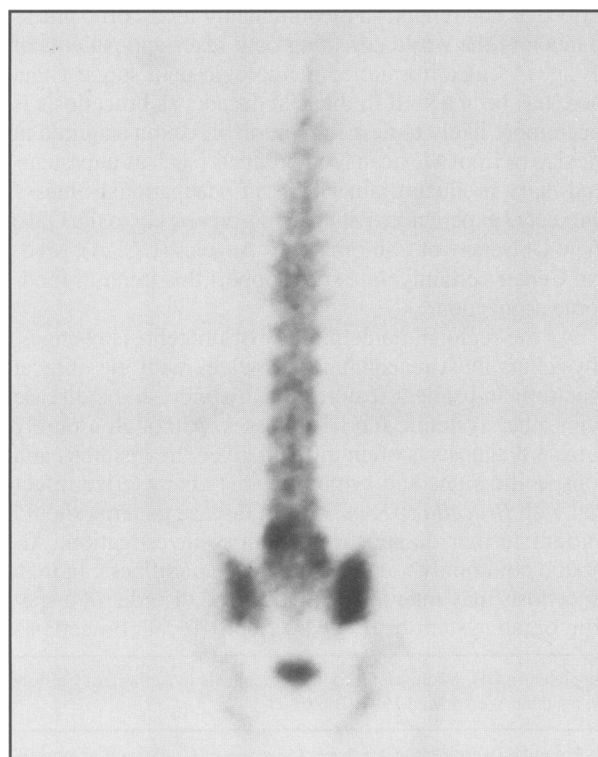
**Discussion***Background and Pathogenesis*

Human brucellosis is a zoonotic infection caused by gram-negative coccobacilli of the genus *Brucella*. Of the six known species of brucellae, only four—*Brucella abortus*, *Brucella melitensis*, *Brucella suis*, and *Brucella canis*—are known to be pathogenic for humans.<sup>1</sup> The primary reservoirs for these species are cattle, goats and sheep, pigs, and dogs, respectively.

Brucellosis is now rarely encountered in the United States and Canada as efforts to decrease its incidence, mainly through surveillance and the quarantine of live-



**Figure 1.**—A magnetic resonance image (sagittal view) depicts L-4 and L-5 spondylitis, accompanying discitis, and the presence of an epidural abscess.



**Figure 2.**—A total body scan (using technetium Tc 99m sulfur colloid) shows increased radiotracer uptake at the L-5 vertebra and the left sacroiliac joint.

stock herds, have been widely successful.<sup>13,6</sup> In fact, bovine brucellosis has been completely eliminated in several countries, including Switzerland, the Czech Republic, Slovakia, Romania, the American Virgin Islands, and Scandinavia.<sup>3</sup> Despite these successes, brucellosis remains endemic in much of the world and is an especially important and costly cause of disease in the Mediterranean, the Middle East, India, and much of Latin America.<sup>1,3</sup>

In most animal hosts, brucellosis presents as a chronic infection that localizes to organs of the genitourinary tract in both sexes and to the udders of the female.<sup>1,3</sup> In most ruminant species (goats, cattle, sheep), this phenomenon reflects the fact that erythritol, a sugar alcohol found in high concentrations within their tissues, is an important growth stimulant for brucellae.<sup>1</sup> Localization to these organs leads to prostatitis, epididymitis, and impotence among infected males and to infertility and abortion among infected females. The organism is thus shed in large quantities in the milk, urine, and products of pregnancy.

The transmission of brucellae from animals to humans almost always occurs through direct contact with infected animals, their contaminated tissues, or their unpasteurized milk products. The disease may be acquired through the contamination of skin wounds or conjunctival surfaces, by inhaling aerosolized microorganisms through the respiratory tract,<sup>12</sup> and more commonly through the digestive tract.<sup>1,5,6</sup> Brucellae are borne in unpasteurized milk and less commonly in raw meat, as well as in dairy products such as butter, cheese, and ice cream.<sup>3</sup> Transmission through the ingestion of unpasteurized dairy products is more likely than through the consumption of raw meat. The microorganism can be transmitted from person to person by blood transfusion, and there is circumstantial evidence of transmission by sexual intercourse.<sup>13</sup>

On infection, a humoral antibody response is mounted as bacteria enter the lymphatics, replicate in local nodes, and become hematogenously disseminated with localization in organs of the reticuloendothelial system. Cellular defense mechanisms play a more important immunologic role, as brucellae are facultative intracellular microorganisms that have the ability to survive within host phagocytes.<sup>1</sup> Brucellosis is systemic in nature, and bacterial infection can involve a wide range of organs and tissues.

### Clinical Disease

Brucellosis can present with acute symptoms but more often manifests as an insidious disease process characterized by a wide variety of chronic and nonspecific signs and symptoms. Somatic complaints dominate, with fever, malaise, sweats, headaches, arthralgia, myalgia, anorexia, and weight loss among the symptoms most commonly reported.<sup>1,6,7,14</sup> Fever appears to be the most consistent feature of the disease, with several patient series reporting its presence in greater than 94% of cases.<sup>1,7,15</sup> A recurrent or "undulating" fever pattern may occur with chronic infection, and brucellosis is often referred to specifically as "undulant fever."<sup>1,3,14</sup>

The physical findings that characterize systemic infection with *Brucella* species are most often nonspecific in

nature, and they may be clinically less prominent than a patient's somatic complaints. Whereas hepatomegaly, splenomegaly, and arthritis are among those most commonly encountered,<sup>1,7,14,15</sup> these findings do not possess much diagnostic value. Laboratory abnormalities associated with brucellosis include anemia, leukopenia, and thrombocytopenia, with leukopenia considered to be of diagnostic utility.<sup>7,15</sup> In one patient series, leukopenia was reported in 45% of infected patients, but no patients had leukocytosis.<sup>15</sup>

Although a systemic illness, brucellosis often manifests clinically as a localized involvement of a specific organ system or tissue.<sup>1,7-9</sup> Localized or "focal" brucellosis is known to occur in practically every organ system and tissue and most frequently involves osteoarticular structures, the central nervous system, the heart, the liver, and the spleen.<sup>1</sup> A broad clinical spectrum is encompassed by such focal disease and includes such disparate disorders as arthritis, spondylitis, meningitis, endocarditis, epididymo-orchitis, and hepatitis. The signs and symptoms of localized disease are clinically related to the affected organ system. It is notable that *Brucella* species endocarditis, although relatively rare, is difficult to treat and accounts for most of the mortality related to the disease.<sup>16</sup>

Interestingly, brucellosis does not predominantly involve the human genitourinary tract, although this is the principal manifestation of *Brucella* species infection in many animals. The human genitourinary tract does not have important levels of erythritol.<sup>1</sup> Although brucellosis can cause abortion in women, there is no evidence that the infection increases the incidence beyond that seen with other more common bacterial infections.<sup>17</sup>

### Osteoarticular Manifestations

The involvement of osteoarticular structures is a particularly prominent and well-studied feature of human brucellosis, occurring in 25% to 34% of cases.<sup>7,10</sup> Localized osteoarticular manifestations of disease include arthritis, bursitis, sacroiliitis, spondylitis, and clinically unmistakable osteomyelitis. Of 304 patients with *Brucella* species infection in one large case series, 103 had articular involvement with their disease, with four distinct articular syndromes: sacroiliitis (46%), peripheral arthritis (39%), mixed arthritis (8%), and spondylitis (6%).<sup>7</sup> The sacroiliac joint was the most commonly involved site in other case series as well,<sup>11</sup> but disease localized to the lumbar spine was more frequently encountered than in the aforementioned study.<sup>8,10,14</sup>

*Brucella* spondylitis deserves some attention because it may mimic spinal tuberculosis (Pott's disease) or may be clinically confused with disc herniation, leading to inappropriate treatment and increased morbidity.<sup>7,14</sup> Spondylitis is usually seen among more elderly patients,<sup>1,7</sup> most commonly involves the lumbar vertebrae,<sup>7,8</sup> and may be complicated by paravertebral abscesses.<sup>1,7,8,14</sup> In regions where the disease is endemic, brucellosis should be considered in the diagnosis of any patient with prolonged fever, musculoskeletal pain, and specifically backache.<sup>11</sup> Tuberculosis must be considered, but can be distin-

guished from *Brucella* species spondylitis by radiographic criteria.<sup>11,14</sup>

### Laboratory Diagnosis

The definitive diagnosis of brucellosis may be made by culturing the organism from blood, bone marrow, or other tissues when they are involved in localized disease. Cultures from bone marrow may have a higher sensitivity and yield than those from blood.<sup>18</sup> Culturing *Brucella* species is notoriously difficult, however, because the bacteria grows slowly.<sup>9</sup> The commonly employed Castaneda technique, which uses a biphasic culture medium, improves bacterial growth, but still may not yield positive cultures until after more than 21 days of incubation.<sup>1</sup> Given the cost of extended incubation and monitoring, many laboratories dispose of negative cultures after a week unless alerted to the suspicion for slow-growing organisms such as *Brucella* species (N. Glover, PhD, Clinical Microbiology Laboratory, Olive View-UCLA Medical Center, oral communication, January 1996). Automated blood culture detection systems (for example, BACTEC), in wide use among larger laboratories, can continuously monitor for culture positivity and allow for an earlier detection of microbial growth.

Given the difficulty of bacterial culture, serologic testing is important to the presumptive diagnosis of brucellosis. The serum agglutination test, the most widely used serologic technique, measures and quantifies serum antibodies directed against the organism. The antigen used in this test will cross-react with *B melitensis*, *B abortus*, and *B suis*, but cannot be used for the serodiagnosis of *B canis*. Antibody titers, when greater than 1:160 or increased fourfold from baseline, are useful in the presumptive diagnosis of *Brucella* species infection.<sup>19</sup> Similarly, decreasing titers can be used to monitor clinical improvement and response to antibiotic therapy.<sup>1</sup> False-positive results with this technique are known to occur as antibodies to other gram-negative bacteria show serologic cross-reactivity. Although false-negative results are often preventable by the dilution of inhibitory factors,<sup>1</sup> there have been reports of seronegative patients with culture-positive brucellosis.<sup>9</sup> Although several other serologic tests are available (rose bengal test, complement fixation, Card test), none have proved to have clinical use superior to the serum agglutination test.<sup>1</sup>

### Treatment

The treatment of brucellosis focuses on the use of combination antibiotics that are capable of diffusing through tissues and achieving adequate intracellular concentrations.<sup>1,19</sup> The current recommendations of the World Health Organization and Food and Agriculture Organization Expert Committee on Brucellosis for treating adult brucellosis is an oral regimen of doxycycline (200 mg per day) plus rifampin (600 to 900 mg per day) for six weeks.<sup>20</sup> In practice, streptomycin is commonly added to the above regimen because studies have shown that the drug increases the rate of bacterial killing.<sup>21</sup>

Currently available fluoroquinolones (such as cipro-

floxacin) lack effective bactericidal activity under intracellular conditions and should not be considered as adequate monotherapy for brucellosis.<sup>22</sup> Clinafloxacin, a newer fluoroquinolone, exhibits more in vitro activity against *Brucella* species and may prove to be of future clinical use.<sup>22</sup> Recent studies have indicated that the use of quinolones plus rifampin for six weeks may be as effective as that of doxycycline plus rifampin given for the same time period.<sup>23</sup> Ceftriaxone given intramuscularly daily for two weeks has been shown to be inadequate treatment of brucellosis.<sup>24</sup>

### Summary

Dynamic changes in patient demography that are currently altering the regional epidemiology of brucellosis attest to the need for physicians to reacquaint themselves with a disease that has been largely forgotten in the United States. This is especially the case in California, which has a large immigrant population and where brucellosis clearly appears to have evolved from an occupational to a food-borne illness. In our recent clinical experiences with several cases of brucellosis, food-borne transmission of the organism is the presumptive cause of the disease, as no cases were associated with occupational risks for exposure to the organism. This suggests that given a clinical history consistent with brucellosis, physicians working with patient groups at risk for food-borne exposure must inquire about the ingestion of unpasteurized dairy products specifically and early during the patient visit. A history of travel to areas endemic for brucellosis may further aid diagnosis.

Although a predominance of nonspecific clinical signs and symptoms (such as fevers or arthralgias) often makes the clinical diagnosis difficult, the frequency and characteristic patterns of localized disease should heighten clinicians' index of suspicion and lower the threshold for a serologic investigation. Prominent musculoskeletal complaints (especially back pain) accompanied by constitutional symptoms such as fever, malaise, and weight loss may be consistent with brucellosis, and a history of unpasteurized dairy ingestion should be elicited. Radiographic evidence that localizes the source of back pain as caused by sacroiliitis or spondylitis is highly suggestive of brucellosis in appropriate patients. In such cases, serologic tests should be pursued early if warranted by the clinical impression.

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## Tumor Implantation at Port Site of Video-Assisted Thoracoscopic Resection of Pulmonary Metastasis

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VIDEO-ASSISTED thoracoscopic surgery is being used with increasing frequency by thoracic surgeons to treat intrathoracic disease. This approach offers the clear advantage over open thoracotomy of less postoperative pain and

(Wille GA, Gregory R, Guernsey JM: Tumor implantation at port site of video-assisted thoracoscopic resection of pulmonary metastasis. *West J Med* 1997; 166:65–66)

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an earlier return to preprocedure levels of activity.<sup>1</sup> Early experience indicates that the two approaches are equally effective when used to treat benign pleural or pulmonary disease, but two concerns are evident when video-assisted thoracoscopic surgery is used to treat malignant parenchymal problems.<sup>2,3</sup> First, video-assisted thoracoscopy precludes a complete examination of the lung that is essential to detect synchronous nodules.<sup>4</sup> Second, there is a growing number of reports of port-site tumor implantation noted during the follow-up period.

We present the cases of three patients with port-site tumor implantation following the wedge resection of pulmonary metastasis by the video-assisted thoracoscopic surgery approach. We also discuss the comparative effectiveness of the two approaches in the surgical treatment of metastasis to the lungs.

### Reports of Cases

#### Patient 1

The patient, a 66-year-old woman, was referred for the surgical evaluation of a 1.5-cm cavitary right upper lobe nodule. Thirty years previously, she had undergone a right total parotidectomy and radical neck dissection for a mucoepidermoid carcinoma and, ten years previously, radiation treatment of a local recurrence. A fine-needle aspiration biopsy showed adenocarcinoma. She underwent a video-assisted stapled wedge resection with the use of three incisions. The mass was not placed in a plastic bag before removal and was removed through the middle incision. The chest tube was brought out through the anterior incision. The surgical margins were free of tumor, there was no spillage, and saline solution was used to irrigate the thoracic cavity. Five months later, chest wall recurrence developed at the camera port site. The chest wall was resected, and she was given adjuvant radiotherapy. Her disease has subsequently recurred, and she has elected not to undergo further treatment.

#### Patient 2

The patient, a 20-year-old man, was seen 24 months after a right above-the-knee amputation for osteogenic sarcoma of the proximal tibia. A chest x-ray film at that time showed three pulmonary nodules measuring between 1 and 2 cm, two on the right and one on the left. They were removed using a video-assisted thoracoscopic approach. Two were excised with electrocautery and a visceral pleural closure. The third was excised using the linear stapling device. The specimens were not placed in a plastic bag before being extracted. The pathologic margins were free of tumor, and the pleural cavities were irrigated with saline solution. Five months later, the patient presented with a mass in the central right port site and a new right parenchymal lung nodule. He died two months later of uncontrolled right thoracic tumor recurrence.

#### Patient 3

The patient, a 40-year-old man, underwent colectomy for poorly differentiated colon carcinoma, stage T2N2M0.